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Stereoselective Synthesis of the C_5–C_{18} Fragment of Halichomycin

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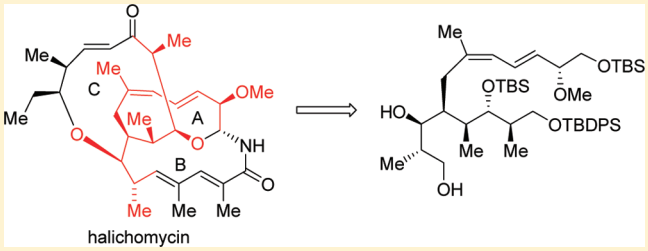
Supporting Information

ABSTRACT: An efficient and convergent synthesis of the C_5–C_{18} fragment of halichomycin is reported. Butanolide fragment **6** was readily prepared stereoselectively from (*R*)-Roche ester through catalyst control; dienylic bromide domain **7** was synthesized from (*S*)-serine by substrate control. C_5–C_{18} fragment **2** was rapidly assembled through a stereoselective alkylation of the butanolide with the dienylic bromide, followed by functional group transformations.



Halichomycin, a structurally unique tricyclic macrolactam, is produced by a strain of *Streptomyces hygroscopicus* which was isolated from the gastrointestinal tract of the marine fish *Halichoeres bleekeri* by Numata and colleagues in 1994 (Figure 1).[1] Halichomycin exhibits potent cytotoxicity (ED_{50} 0.13 μg/mL) against a murine P388 lymphocytic leukemia cell line, which is of potential use as an anticancer drug.

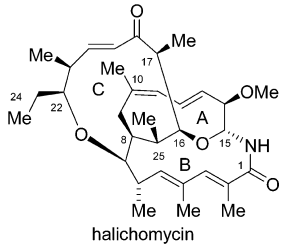


Figure 1. Structure of halichomycin (relative configuration).

Halichomycin represents a significant challenge to chemical synthesis owing to its extraordinary molecular architecture, embodying three intersecting ring systems which include a fully functionalized 11-membered ether ring (C ring) and a structurally unique 13/11-membered bicyclic hemimacrolactam (AB ring), 10 stereocenters including six contiguous stereocenters, and five double bonds. However, the absolute configuration of halichomycin has not been reported until now. The unique structural features and powerful biological activity of **1** make it an attractive target for total synthesis.[2] Wood reported the synthesis of the C_1–C_7 segment of halichomycin.[2a] Hale proposed a biosynthetic route for ring formation in halichomycin and synthesized the AB-carbon backbone of halichomycin.[2b] However, no total synthesis has been accomplished up to now. As part of our interest directed toward the total synthesis of bioactive natural products,[3] we have embarked on the synthesis of halichomycin. In order to test the formation of the "strange"[4] hemimacrolactam of halichomycin, a concise and scalable synthesis of its backbone is needed. Herein, we report a synthetic strategy for the C_5–C_{18} fragment (**2**), which includes six contiguous stereocenters.

Our retrosynthetic analysis of halichomycin (**1**) is outlined in Scheme 1. The key compound **2** could be generated from an Evans asymmetric aldol reaction between aldehyde **3** and acylated oxazolidinone **4** followed by reduction. In order to introduce with stereocontrol the C_8 and C_{25} vicinal carbon substituents of **3**, butenolide **8** was used as the chiral template.[5] The lactone **5** could be obtained through stereoselective *α*-alkylation of **6** with bromide **7** from the *β*-face. Butyrolactone **6** could be accessed by conjugate addition of lithium dimethylcuprate to butenolide **8**, which would be available from the Pu asymmetric addition of methyl propiolate to aldehydes,[6] followed by Lindlar reduction. Dienylic bromide **7** would be obtained in optically pure form by manipulation of chiron derived originally from (*S*)-serine.

The synthesis of the known lactone **6** has been reported by many other groups.[7] We developed a new method for the synthesis of **6** (Scheme 2). The known aldehyde **12** was prepared in 95% yield starting from the commercially available (*R*)-Roche ester **9**.[8] According to the standard conditions reported by Pu, the (*S*)-BINOL-catalyzed asymmetric addition of ethyl propiolate **10** to aldehyde **12** led to the desired product **13** in 94% yield with a diastereomeric ratio of 11:1, which was impossible to separate by column chromatography.[9] Lindlar reduction of alkyne **13** gave the corresponding *cis*-alkene, which was automatically converted into butenolide **8** during purification by flash column chromatography. Conjugate addition of Me_2CuLi to butenolide **8** gave the known exclusive product lactone **6**[2b,7e] as a single stereoisomer in 85% yield.

The synthesis of C_9–C_{15} dienylic bromide **7** is shown in Scheme 3. The known alcohol **15** was prepared from (*S*)-serine

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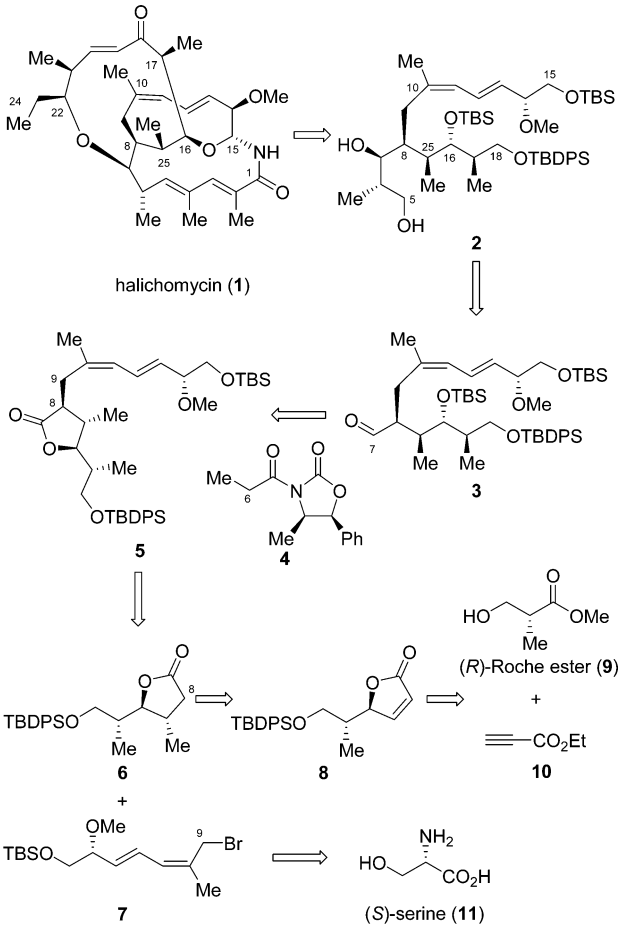
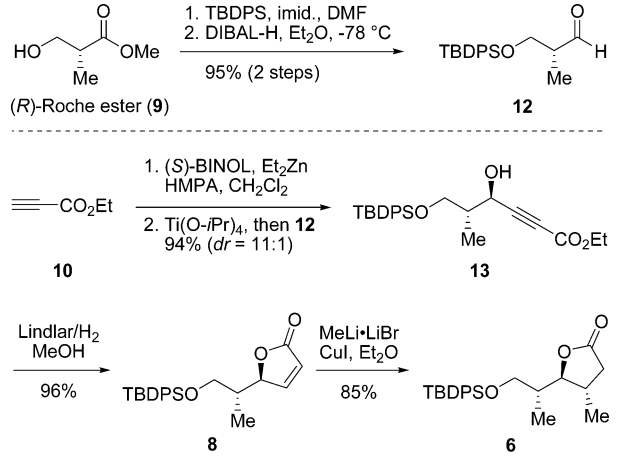
Scheme 1. Retrosynthetic Analysis of Halichomycin (1)

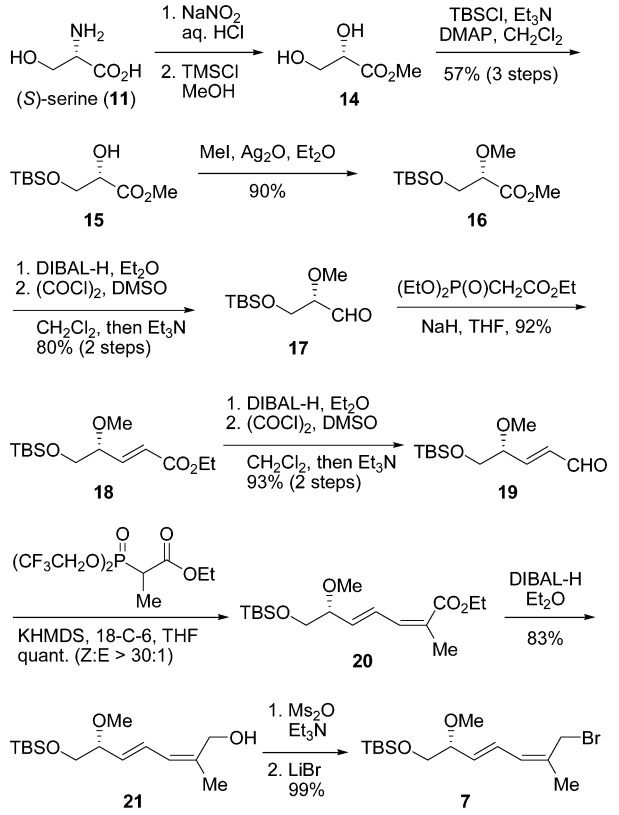


Scheme 2. Synthesis of Lactone 6



(**11**) in 57% overall yield.[10] Methylation of alcohol **15** with iodomethane and Ag_2O in Et_2O afforded **16** in 90% yield.[11,12] DIBAL reduction of the ester moiety in **16** followed by Swern oxidation of the derived alcohol provided aldehyde **17** in 80% yield, which further underwent a Horner–Wadsworth–Emmons olefination to afford **18** in 92% yield. DIBAL reduction of ester **18** followed by Swern oxidation provided the aldehyde **19** in 93% yield. (*Z*)-Selective olefination of aldehyde **19** using Still–Gennari's protocol provided diene **20** in quantitative yield.[13,14] Reduction of ester **20** with DIBAL gave the corresponding allylic alcohol **21**, which was subjected

Scheme 3. Synthesis of Dienylic Bromide 7



to bromination following Roush's procedure to afford the dienylic bromide **7** in 99% yield.[15]

With the two fragments **6** and **7** in hand, the stage was set for the key α-alkylation reaction (Scheme 4). It smoothly afforded the desired coupling product **5** as a nearly 4.2:1[16] inseparable diastereomers. It is worth mentioning that HMPA played an important role in this reaction, giving a higher conversion. Lactone **5** was reductively ring-opened with lithium borohydride to produce the diol **22** in 60% overall yield. Selective protection of the primary alcohol in **22** by using Ac_2O/DMAP, followed by protection the remaining secondary hydroxy group by using TBSOTf/2,6-lutidine, furnished fully protected compound **23** in 94% overall yield. Removal of the acetyl group in **23** employing K_2CO_3 in CH_3OH followed by IBX oxidation of the derived alcohol **24** provided aldehyde **3** in 96% yield. In order to promote the complete conversion of aldehyde **3** in the Evans aldol reaction,[17] it was essential to use the excess of propionimide enolate (see the Experimental Section). Finally, reductive removal of the oxazolidinone unit from **25** with $LiBH_4$ furnished the diol **2** in 95% yield.[18]

In conclusion, we have accomplished the synthesis of the C_5–C_{18} fragment (**2**) of halichomycin. The approach is highly convergent. The longest linear sequence is 20 steps, and the overall yield is an impressive 8.8%. The synthesis features an (*S*)-BINOL-catalyzed asymmetric addition of ethyl propiolate to aldehyde followed by reduction to form the butenolide **8**, and stereocontrolled introduction of C_8 and C_{25} functional groups by using butenolide **8** as the chiral template.

■ EXPERIMENTAL SECTION

General Remarks. Flash column chromatography (FCC) was performed using silica gel (200–300 mesh) with solvents distilled prior to use. Petroleum ether is abbreviated to PE.

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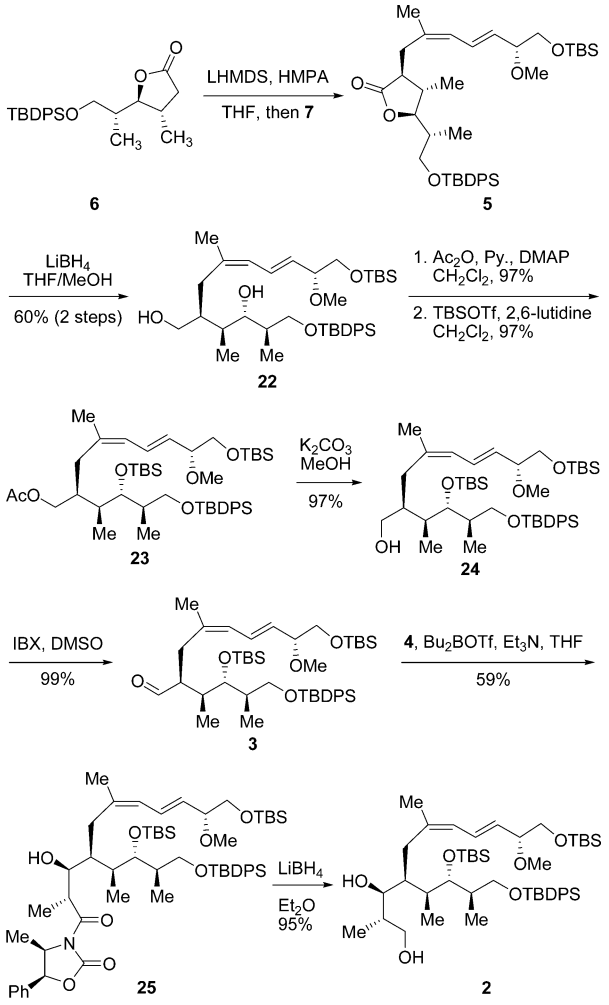
Scheme 4. Synthesis of Fragment 2



Compound 13. To a solution of (*S*)-BINOL (458 mg, 1.6 mmol), HMPA (1.4 mL, 8.0 mmol), and ethyl propiolate (1.63 mL, 16.0 mmol) in dry CH_2Cl_2 (48 mL) at rt under Ar was added Et_2Zn (16 mL, 1 M in hexane, 16.0 mmol). After the solution had been stirred for 16 h, Ti(O-*i*-Pr)$_4$ (1.2 mL, 4.0 mmol) was added and stirred for another 1 h. Then, **12** (1.30 g, 4.0 mmol) was added, and the reaction was allowed to proceed at rt for 4 h. The mixture was quenched with saturated NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by FCC (PE/EtOAc, 12:1) to give the product **13** (1.59 g, 94%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.67 (m, 4H), 7.46−7.39 (m, 6H), 4.65 (t, J = 6.0 Hz, 1H), 4.26 (q, J = 7.2 Hz, 2H), 3.96 (dd, J = 4.0, 10.4 Hz, 1H), 3.63 (dd, J = 6.0, 10.4 Hz, 1H), 3.49 (d, J = 5.2 Hz, 1H), 2.07 (m, 1H), 1.33 (t, J = 7.2 Hz, 3H), 1.08 (d, J = 6.8 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 135.6, 135.5, 132.7, 132.6, 129.9, 127.8, 86.8, 77.4, 66.8, 66.1, 62.0, 40.4, 26.8, 19.1, 14.0, 12.9; HRMS (ESI) m/z calcd for $C_{25}H_{33}O_4Si$ (M + H)$^+$ 425.2143, found 425.2138; IR (KBr) 3032, 2961, 2859, 2234, 1713, 1470, 1427, 1390, 1366, 1246, 1110, 1037, 823, 742, 704, 614, 505 cm^{-1}.

Compound 8. To a solution of **13** (936 mg, 2.21 mmol) in methanol (30 mL) was added Lindlar catalyst (221 mg) at rt, and then the flask was evacuated and filled with hydrogen three times. The suspension was stirred under H_2 at rt for 11 h and then filtered through a pad of Celite and concentrated. The residue was purified by FCC (PE/EtOAc, 10:1) to give butenolide **8** (805 mg, 96%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67−7.63 (m, 4H), 7.47−7.38 (m, 7H), 6.11 (dd, J = 1.6, 5.6 Hz, 1H), 5.23 (dt, J = 1.6, 6.0 Hz, 1H), 3.81 (dd, J = 4.4, 10.4 Hz, 1H), 3.59 (dd, J = 6.0, 10.4 Hz, 1H), 2.16 (m, 1H), 1.07 (s, 9H), 0.90 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 155.3, 135.6, 135.5, 133.1, 133.0, 129.9, 129.8, 127.8, 121.9, 84.6, 65.1, 39.2, 26.9, 19.3, 11.7; $[\alpha]_D^{26}$ −37.6 (c 1.07, MeOH); HRMS (ESI) m/z calcd for $C_{23}H_{32}NO_3Si$ (M + NH_4)$^+$ 398.2146, found 398.2149; IR (KBr) 2959, 2931, 2858, 1784, 1757, 1471, 1428, 1162, 1110, 1089, 1029, 820, 742, 704, 614, 505 cm^{-1}.

Compound 6. To a slurry of CuI (1.72 g, 9.05 mmol) in Et_2O (25 mL) was added MeLi·LiBr (10.9 mL, 1.5 M in ether, 16.2 mmol) at 0 °C under Ar. The solution was cooled to −30 °C, and then **8** (686 mg, 1.81 mmol) in Et_2O (5 mL) was added. The mixture was stirred at −20 °C for 1 h and quenched with saturated NH_4Cl. Ammonium hydroxide was added, and the aqueous layers were extracted with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by FCC (PE/EtOAc, 6:1) to give **6** (609 mg, 85%). The data of ^{1}H and ^{13}C NMR are consistent with that reported by Hale:[2b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.66 (m, 4H), 7.46−7.37 (m, 6H), 4.15 (t, J = 6.4 Hz, 1H), 3.70 (dd, J = 1.6, 5.2 Hz, 2H), 2.68 (dd, J = 8.8, 17.2 Hz, 1H), 2.49 (m, 1H), 2.18 (dd, J = 8.0, 17.6 Hz, 1H), 1.99 (m, 1H), 1.17 (d, J = 6.8 Hz, 3H), 1.08 (s, 9H), 1.01 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 135.5, 133.4, 133.3, 129.7, 127.7, 88.3, 64.9, 39.4, 37.1, 32.2, 26.8, 19.3, 19.2, 13.0; $[\alpha]_D^{26}$ +23.9 (c 0.50, MeOH); HRMS (ESI) m/z calcd for $C_{24}H_{36}NO_3Si$ (M + NH_4)$^+$ 414.2459, found 414.2453; IR (KBr) 2960, 2929, 2857, 1779, 1463, 1427, 1214, 1173, 1110, 1007, 823, 742, 704, 614, 505 cm^{-1}.

Compound 16. To a solution of **15** (5.86 g, 25.0 mmol), MeI (31 mL, 500 mmol) in Et_2O (300 mL) was added Ag_2O (17.4 g, 75.0 mmol). The reaction mixture was stirred for 10 h at rt, filtered, and concentrated, and the residue was purified by FCC (PE/EtOAc, 8:1) to give **16** (5.6 g, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 3.72 (s, 3H), 3.41 (s, 3H), 0.84 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 82.0, 64.0, 58.5, 51.7, 25.7, 18.2, −5.5, −5.6; $[\alpha]_D^{23}$ −24.3 (c 0.40, CH_2Cl_2), *the optical rotation of its enantiomer* [lit.[11] $[\alpha]_D^{28}$ +20.3 (c 1.9, CH_2Cl_2)]; HRMS (ESI) m/z calcd for $C_{11}H_{24}O_4SiNa$ (M + Na)$^+$ 271.1336, found 271.1333; IR (KBr) 2954, 2931, 2858, 1756, 1464, 1257, 1201, 1121, 839, 779 cm^{-1}.

Compound 17. To a solution of **16** (4.02 g, 16.2 mmol) in Et_2O (110 mL) at −78 °C was added DIBAL-H (19.5 mL, 1 M in hexane, 19.5 mmol). After the starting material was consumed via TLC analysis, the reaction was quenched with MeOH, warmed to rt, and poured into satd aq potassium sodium tartrate solution. The mixture was vigorously stirred until the phase separation occurred and extracted with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated to give the corresponding alcohol.

To a solution of $(COCl)_2$ (2.9 mL, 32.4 mmol) in CH_2Cl_2 (120 mL) at −78 °C was added DMSO (4.6 mL, 64.8 mmol). After being stirred for 10 min, the alcohol was added to CH_2Cl_2 (15 mL). After 45 min, Et_3N (13.6 mL, 97.2 mmol) was added, and the solution was warmed to rt. After 30 min, the reaction was quenched with water and extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by FCC (PE/EtOAc, 20:1) to give the aldehyde **17** (2.83 g, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 3.91 (d, J = 4.4 Hz, 2H), 3.66 (t, J = 4.4 Hz, 1H), 3.50 (s, 3H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.9, 86.5, 62.5, 58.6, 25.8, 18.3, −5.5; $[\alpha]_D^{22}$ −32.0 (c 0.40, CH_2Cl_2); HRMS (ESI) m/z calcd for $C_{10}H_{23}O_3Si$ (M + H)$^+$ 219.1411, found 219.1411; IR (KBr) 2954, 2931, 2858, 1737, 1467, 1256, 1114, 838, 778 cm^{-1}.

Compound 18. To a solution of NaH (524 mg, 13.1 mmol, 60% in mineral oil) in THF (25 mL) at 0 °C was added triethyl phosphonoacetate (2.62 mL, 13.2 mmol). After being stirred for 10 min, aldehyde **17** (2.62 g, 12.0 mmol) in THF (5 mL) was added. The reaction mixture was warmed to rt and then heated at reflux for 1 h. The solution was cooled to rt, diluted with water, and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by FCC (PE/EtOAc, 40:1) to give **18** (3.18 g, 92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (dd, J = 5.6, 16.0 Hz, 1H), 6.02 (dd, J = 1.2, 16.0 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.82 (m, 1H), 3.67 (dd, J = 6.0, 10.4 Hz,

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1H), 3.58 (dd, J = 5.6, 10.4 Hz, 1H), 3.35 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 145.4, 122.8, 81.5, 65.3, 60.3, 57.7, 25.8, 18.2, 14.2, −5.4, −5.5; $[\alpha]_D^{25}$ −8.0 (c 0.43, CH_2Cl_2); HRMS (ESI) m/z calcd for $C_{14}H_{32}NO_4Si$ $(M + NH_4)^+$ 306.2095, found 306.2089; IR (KBr) 2955, 2931, 2859, 1724, 1660, 1467, 1366, 1303, 1261, 1172, 1137, 1114, 1041, 984, 839, 779 cm^{-1}.

Compound 19. The ester **18** (1.37 g, 4.76 mmol) was converted into aldehyde **19** (1.08 g, 93% for two steps) by DIBAL reduction and Swern oxidation of the corresponding alcohol as described for compound **17**.

Corresponding alcohol S2: $[\alpha]_D^{23}$ −15.7 (c 0.38, CH_2Cl_2); HRMS (ESI) m/z calcd for $C_{12}H_{27}O_3Si$ $(M + H)^+$ 247.1724, found 247.1724; IR (KBr) 3416, 2954, 2930, 2858, 1464, 1255, 1096, 838, 777 cm^{-1}.

19: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (dd, J = 1.2, 8.0 Hz, 1H), 6.72 (dd, J = 5.6, 16.0 Hz, 1H), 6.26 (ddd, J = 1.2, 8.0, 16.0 Hz, 1H), 3.92 (dd, J = 5.2, 10.8 Hz, 1H), 3.72 (m, 1H), 3.59 (dd, J = 6.0, 10.4 Hz, 1H), 3.34 (s, 3H), 0.83 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.0, 154.4, 132.9, 81.3, 64.8, 57.8, 25.7, 18.1, −5.5, −5.6; $[\alpha]_D^{22}$ +14.4 (c 0.32, CH_2Cl_2); HRMS (ESI) m/z calcd for $C_{12}H_{28}NO_3Si$ $(M + NH_4)^+$ 262.1833, found 262.1831; IR (KBr) 2957, 2931, 2858, 1724, 1696, 1468, 1256, 1117, 980, 839, 779 cm^{-1}.

Compound 20. To a solution of ethyl 2-[bis(2,2,2-trifluoroethyl) phosphono]propionate (1.15 g, 3.33 mmol) and 18-crown-6 (3.38 g, 12.8 mmol) in THF (50 mL) at −78 °C was added KHMDS (6.15 mL, 0.5 M in toluene, 3.07 mmol) under Ar. After the solution was stirred for 1 h, aldehyde **19** (624 mg, 2.56 mmol) in THF (5 mL) was added. The reaction mixture was stirred for another 1 h, quenched with saturated NH_4Cl, and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by FCC (PE/EtOAc, 30:1) to give **20** (840 mg, quant, Z:E > 30:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, J = 11.2, 15.2 Hz, 1H), 6.37 (d, J = 11.2 Hz, 1H), 5.69 (dd, J = 7.2, 15.2 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.72 (m, 1H), 3.64 (dd, J = 6.4, 10.4 Hz, 1H), 3.56 (dd, J = 5.2, 10.4 Hz, 1H), 3.29 (s, 3H), 1.93 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H), 0.84 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 138.8, 137.0, 130.0, 126.9, 82.7, 66.0, 60.2, 56.9, 25.8, 20.6, 18.2, 14.1, −5.3, −5.4; $[\alpha]_D^{23}$ −23.0 (c 0.49, CH_2Cl_2); HRMS (ESI) m/z calcd for $C_{17}H_{36}NO_4Si$ $(M + NH_4)^+$ 346.2408, found 346.2416; IR (KBr) 2954, 2929, 2858, 1712, 1464, 1377,1255, 1209, 1162, 1108, 838, 777 cm^{-1}.

Compound 21. DIBAL reduction of **20** (867 mg, 2.64 mol) gave **21** (624 mg, 83%) described as above: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (dd, J = 11.2, 15.2 Hz, 1H), 5.93 (d, J = 11.2 Hz, 1H), 5.47 (dd, J = 7.2, 15.2 Hz, 1H), 4.24 (d, J = 2.8 Hz, 2H), 3.70−3.62 (m, 2H), 3.55 (dd, J = 4.8, 10.4 Hz, 1H), 3.31 (s, 3H), 1.86 (s, 3H), 1.75 (brs, 1H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 130.6, 128.1, 127.1, 83.0, 66.2, 61.5, 56.9, 25.9, 21.4, 18.3, −5.3 (2C); $[\alpha]_D^{24}$ −28.6 (c 0.48, CH_2Cl_2); HRMS (ESI) m/z calcd for $C_{15}H_{31}O_3Si$ $(M + H)^+$ 287.2037, found 287.2034; IR (KBr) 3418, 2953, 2929, 2858, 1466, 1254, 1111, 1007, 969, 838, 778 cm^{-1}.

Compound 7. To a stirred solution of **21** (572 mg, 2.0 mmol) and triethylamine (0.44 mL, 3.0 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added Me_2O (453 mg, 2.6 mmol). After 15 min, the reaction was diluted with acetone (4 mL) and charged with LiBr (1.05 g, 12.0 mmol). After the mixture was stirred for 1.5 h at 25 °C, the solvents were removed in vacuo. The concentrate was then rinsed out of the flask and partitioned between saturated NH_4Cl and EtOAc. The aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by FCC (PE/EtOAc, 20:1) to give **7** (691 mg, 99%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (dd, J = 11.2, 15.2 Hz, 1H), 5.99 (d, J = 10.8 Hz, 1H), 5.61 (dd, J = 7.2, 15.2 Hz, 1H), 4.11 (dd, J = 10.0, 13.2 Hz, 2H), 3.76−3.65 (m, 2H), 3.58 (dd, J = 4.8, 10.0 Hz, 1H), 3.34 (s, 3H), 1.92 (s, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.6, 132.5, 129.5, 127.6, 82.9, 66.0, 57.1, 31.9, 25.9, 22.1, 18.4, −5.2, −5.3; $[\alpha]_D^{21}$ −24.0 (c 0.20, CH_2Cl_2); HRMS (ESI) m/z calcd for $C_{15}H_{33}NBrO_2Si$ $(M + NH_4)^+$ 366.1458, found 366.1463; IR (KBr) 2954, 2928, 2856, 1254, 1134, 1110, 838, 777 cm^{-1}.

Compound 22. To a solution of **6** (522 mg, 1.32 mmol) and HMPA (0.46 mL, 2.64 mmol) in THF (30 mL) under Ar at −78 °C was added LHMDS (2.64 mL, 1.0 M in THF, 2.64 mmol). The solution was stirred at −78 °C for 1 h, and **7** (552 mg, 1.58 mmol) in THF (5 mL) was added. After 45 min, the reaction mixture was quenched with saturated $NaHCO_3$, and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by FCC (PE/EtOAc, 15:1) to give the inseparable coupling product **5** and its isomers (781 mg, 89% overall yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.63 (m, 4H), 7.44−7.36 (m, 6H), 6.44 (dd, J = 12.0, 14.0 Hz, 1H), 5.97 (d, J = 10.8 Hz, 1H), 5.48 (dd, J = 6.4, 14.8 Hz, 1H), 4.03 (t, J = 7.2 Hz, 1H), 3.69−3.56 (m, 5H), 3.29 (s, 3H), 2.68 (m, 1H), 2.51−2.37 (m, 2H), 2.12−1.96 (m, 2H), 1.79 (s, 3H), 1.11 (d, J = 6.0 Hz, 3H), 1.05 (s, 9H), 0.98 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 135.5, 135.4, 133.5, 133.4, 130.1, 129.7, 128.5, 127.7, 127.6, 85.8, 83.2, 66.4, 65.0, 56.8, 46.7, 39.7, 38.7, 32.0, 26.9, 25.9, 23.7, 19.3, 18.4, 18.1, 13.1, −5.2, −5.3; HRMS (ESI) m/z calcd for $C_{39}H_{64}NO_5Si_2$ $(M + NH_4)^+$ 682.4318, found 682.4329.

To a stirred solution of **5** (781 mg, 1.17 mmol) in THF (20 mL) and MeOH (0.2 mL) at 0 °C was added $LiBH_4$ (257 mg, 11.7 mmol). The reaction mixture was warmed to rt, stirred for 1.5 h, cooled to 0 °C, carefully quenched with HCl (1.0 M), and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by FCC (PE/EtOAc, 8:1) to give **22** (530 mg, 67%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.68 (m, 4H), 7.47−7.39 (m, 6H), 6.51 (dd, J = 11.2, 14.8 Hz, 1H), 5.93 (d, J = 11.2 Hz, 1H), 5.42 (dd, J = 7.2, 14.8 Hz, 1H), 3.93 (dd, J = 3.2, 10.4 Hz, 1H), 3.74−3.41 (m, 8H), 3.32 (s, 3H), 2.36−2.16 (m, 3H), 2.06−1.92 (m, 3H), 1.86 (s, 3H), 1.11 (d, J = 6.8 Hz, 3H), 1.07 (s, 9H), 0.91 (s, 9H), 0.86 (d, J = 7.2 Hz, 3H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 135.6, 135.5, 132.6, 132.5, 129.9, 129.5, 128.5, 127.8, 127.7, 126.0, 83.3, 79.3, 67.2, 66.5, 64.0, 56.7, 39.4, 36.8, 35.9, 30.1, 26.8, 25.9, 24.0, 19.0, 18.4, 15.3, 12.5, −5.2, −5.3; $[\alpha]_D^{23}$ −21.6 (c 0.43, CH_2Cl_2); HRMS (ESI) m/z calcd for $C_{39}H_{64}O_5Si_2Na$ $(M + Na)^+$ 691.4184, found 691.4199; IR (KBr) 2956, 2928, 2857, 1469, 1428, 1256, 1110, 1084, 837, 747, 703, 505 cm^{-1}.

Compound 23. To a solution of **22** (339 mg, 0.51 mmol), pyridine (82 μL, 1.02 mmol), and DMAP (12 mg, 0.010 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added Ac_2O (73 μL, 0.77 mmol). The reaction mixture was stirred at rt for 1 h, quenched with saturated NH_4Cl, and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by FCC (PE/EtOAc, 10:1) to give the primary alcohol Ac-protected product **S3** (349 mg, 97%): $[\alpha]_D^{23}$ −13.2 (c 0.26, CH_2Cl_2); HRMS (ESI) m/z calcd for $C_{41}H_{66}O_6Si_2Na$ $(M + Na)^+$ 733.4290, found 733.4282; IR (KBr) 2961, 2928, 2857, 1338, 1260, 1109, 751, 704 cm^{-1}.

To a stirred solution of **S3** (304 mg, 0.43 mmol) and 2,6-lutidine (0.30 mL, 2.58 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added TBSOTf (0.30 mL, 1.29 mmol). The reaction mixture was stirred at rt for 1.5 h, quenched with saturated NH_4Cl, and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by FCC (PE/EtOAc, 20:1) to give **23** (342 mg, 97%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.64 (m, 4H), 7.42−7.33 (m, 6H), 6.40 (dd, J = 11.2, 15.2 Hz, 1H), 5.92 (d, J = 11.2 Hz, 1H), 5.42 (dd, J = 7.2, 15.2 Hz, 1H), 3.94 (dd, J = 3.6, 11.2 Hz, 1H), 3.84−3.58 (m, 6H), 3.44 (dd, J = 8.4, 9.2 Hz, 1H), 3.33 (s, 3H), 2.35−2.21 (m, 2H), 2.11 (m, 1H), 2.01 (m, 1H), 1.97 (s, 3H), 1.87 (m, 1H), 1.78 (s, 3H), 1.06 (s, 9H), 1.00 (dd, J = 3.2, 6.8 Hz, 3H), 0.91 (dd, J = 1.2, 7.2 Hz, 3H), 0.89 (s, 9H), 0.79 (s, 9H), 0.06−0.02 (9H), −0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 137.7, 135.6 (2C), 134.0, 133.9, 129.5 (2C), 129.0, 128.8, 127.6, 126.9, 83.3, 77.8, 66.6 (2C), 64.9, 56.8, 40.2, 36.4, 35.5, 30.5, 26.9, 26.1, 25.9, 23.8, 20.9, 19.3, 18.4, 18.2, 14.5, 13.2, −3.8, −4.4, −5.2, −5.3; $[\alpha]_D^{23}$ +18.2 (c 0.22, CH_2Cl_2); HRMS (ESI) m/z calcd for $C_{47}H_{80}O_6Si_3Na$ $(M + Na)^+$ 847.5155,

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found 847.5152; IR (KBr) 2927, 2856, 1730, 1466, 1262, 1108, 752 cm^{-1}.

Compound 24. To a solution of **23** (313 mg, 0.38 mmol) in MeOH (5 mL) was added K_2CO_3 (262 mg, 1.90 mmol) at rt. After being stirred for 5 h, the reaction was diluted with EtOAc and washed with 0.1 M NaOH (aq) solution. The aqueous layer was extracted with EtOAc, and the combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by FCC (PE/EtOAc, 15:1) to give **24** (290 mg, 97%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.68−7.65 (m, 4H), 7.43−7.34 (m, 6H), 6.47 (dd, J = 11.2, 15.2 Hz, 1H), 5.93 (d, J = 10.8 Hz, 1H), 5.42 (dd, J = 7.2, 15.2 Hz, 1H), 3.85 (dd, J = 5.2, 10.0 Hz, 1H), 3.73−3.43 (m, 6H), 3.35 (dd, J = 6.0, 11.2 Hz, 1H), 3.32 (s, 3H), 2.33 (m, 1H), 2.17 (m, 1H), 2.02 (m, 1H), 1.92−1.90 (m, 2H), 1.80 (s, 3H), 1.07 (s, 9H), 1.03 (d, J = 6.8 Hz, 3H), 0.90 (s, 12H), 0.79 (s, 9H), 0.07−0.03 (9H), −0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 135.7, 134.1, 134.0, 129.5, 129.4, 128.9, 127.6, 126.4, 83.3, 78.1, 66.7, 66.5, 63.7, 56.7, 40.2, 38.9, 36.6, 31.0, 27.0, 26.1, 26.0, 24.0, 19.3, 18.4, 18.2, 14.8, 13.6, −3.7, −4.4, −5.2, −5.3; $[\alpha]_D^{23}$ +10.7 (c 0.21, CH_2Cl_2); HRMS (ESI) m/z calcd for $C_{45}H_{82}NO_5Si_3$ $(M + NH_4)^+$ 800.5495, found 800.5479; IR (KBr) 2955, 2923, 2856, 1463, 1254, 1109, 1033, 1006, 836, 774, 702 cm^{-1}.

Compound 3. To a solution of **24** (221 mg, 0.28 mmol) in DMSO (6 mL) was added IBX (118 mg, 0.42 mmol) at rt. After 2.5 h, the reaction mixture was diluted with water (20 mL), filtered, and extracted with EtOAc. The combined organic extracts were washed with water, brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by FCC (PE/EtOAc, 30:1) to give **3** (216 mg, 99%). ^1H NMR (400 MHz, $CDCl_3$) δ 9.52 (d, J = 2.0 Hz, 1H), 7.65 (d, J = 7.6 Hz, 4H), 7.44−7.35 (m, 6H), 6.46 (dd, J = 11.2, 15.2 Hz, 1H), 5.89 (d, J = 11.2 Hz, 1H), 5.44 (dd, J = 7.2, 15.2 Hz, 1H), 3.79−3.56 (m, 5H), 3.44 (dd, J = 8.0, 10.0 Hz, 1H), 3.33 (s, 3H), 2.67−2.58 (m, 2H), 2.31 (m, 1H), 2.15 (m, 1H), 1.96 (m, 1H), 1.77 (s, 3H), 1.06 (s, 9H), 0.96 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 7.6 Hz, 3H), 0.89 (s, 9H), 0.81 (s, 9H), 0.06−0.03 (9H), −0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.1, 135.9, 135.6, 133.9, 133.8, 129.7, 129.6 (2C), 128.7, 127.6, 126.9, 83.2, 77.2, 66.5, 66.2, 56.9, 50.8, 40.1, 36.7, 29.4, 26.9, 26.0, 25.9, 23.9, 19.2, 18.4, 18.2, 14.3, 13.9, −3.9, −4.4, −5.2, −5.3; $[\alpha]_D^{24}$ +14.2 (c 0.16, CH_2Cl_2); HRMS (ESI) m/z calcd for $C_{45}H_{80}NO_5Si_3$ $(M + NH_4)^+$ 798.5339, found 798.5343; IR (KBr) 2955, 2926, 2855, 1729, 1463, 1256, 1110, 837, 774 cm^{-1}.

Compound 25. To a solution of (4*R*,5*S*)-4-methyl-5-phenyl-3-propionyl-2-oxazolidinone (**4**) (378 mg, 1.62 mmol) in CH_2Cl_2 (5.5 mL) at 0 °C under Ar were successively added Bu_2BOTf (1.62 mL, 1 M in CH_2Cl_2, 1.62 mmol) and triethylamine (0.28 mL, 1.94 mmol). After the solution was stirred at 0 °C for 45 min, **3** (158 mg, 0.202 mmol) in CH_2Cl_2 (2 mL) was added at −78 °C. The resulting mixture was stirred for 1 h, warmed to rt, stirred overnight, and quenched with phosphate buffer (4 mL, pH = 7) followed by addition of MeOH (1 mL). To the resulting slurry was then added slowly 3 mL of a 2:1 v/v mixture of MeOH/30% aq H_2O_2, and the mixture was stirred vigorously for 4 h. The reaction was then extracted with EtOAc, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by FCC (PE/EtOAc, 12:1) to give **25** (121 mg, 59%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.68−7.65 (m, 4H), 7.42−7.34 (m, 9H), 7.22 (d, J = 6.8 Hz, 2H), 6.61 (dd, J = 11.2, 15.2 Hz, 1H), 5.97 (d, J = 10.8 Hz, 1H), 5.55 (d, J = 7.2 Hz, 1H), 5.47 (dd, J = 7.2, 15.2 Hz, 1H), 4.72 (m, 1H), 3.88−3.80 (m, 3H), 3.76−3.58 (m, 4H), 3.45 (t, J = 9.2 Hz, 1H), 3.34 (s, 3H), 2.64 (t, J = 12.8 Hz, 1H), 2.30−2.03 (m, 5H), 1.86 (s, 3H), 1.26 (d, J = 6.4 Hz, 3H), 1.07 (s, 9H), 1.02 (d, J = 7.2 Hz, 3H), 1.00 (d, J = 7.6 Hz, 3H), 0.90 (s, 9H), 0.84 (d, J = 6.4 Hz, 3H), 0.80 (s, 9H), 0.07−0.06 (9H), −0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 152.1, 139.4, 135.6, 135.5, 133.9 (2C), 133.2, 129.5, 129.3, 128.7 (3C), 127.6, 126.7, 125.5, 83.2, 79.2, 78.7, 73.3, 67.0, 66.6, 56.8, 54.6, 41.2, 41.1, 36.1, 34.3, 30.4, 27.0, 26.2, 26.0, 23.7, 19.3, 18.4, 18.3, 14.2 (2C), 14.0, 13.5, −3.3, −4.2, −5.1, −5.3; $[\alpha]_D^{24}$ +21.2 (c 0.44, CH_2Cl_2); HRMS (ESI) m/z calcd for $C_{58}H_{95}N_2O_8Si_3$ $(M + NH_4)^+$ 1031.6391, found 1031.6410; IR (KBr) 2956, 2930, 2857, 1786, 1697, 1462, 1345, 1254, 1194, 1112, 1091, 1027, 836, 774, 702 cm^{-1}.

Compound 2. Compound **2** was prepared from **25** (23 mg, 0.023 mmol) as described for compound **22** in Et_2O/H_2O (160:1): FCC (PE/EtOAc, 6:1), yield (18.3 mg, 95%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.67−7.64 (m, 4H), 7.42−7.35 (m, 6H), 6.50 (dd, J = 10.8, 14.8 Hz, 1H), 5.87 (d, J = 10.8 Hz, 1H), 5.44 (dd, J = 6.8, 14.8 Hz, 1H), 3.80 (dd, J = 6.0, 10.0 Hz, 1H), 3.72−3.56 (m, 7H), 3.45 (t, J = 8.8 Hz, 1H), 3.33 (s, 3H), 2.41−2.01 (m, 7H), 1.82 (s, 3H), 1.77 (m, 1H), 1.06 (s, 9H), 1.01 (d, J = 6.8 Hz, 3H), 0.94−0.89 (m, 15H), 0.79 (s, 9H), 0.06−0.05 (9H), −0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 135.6, 133.9 (2C), 129.5, 129.2, 128.8, 127.6, 126.1, 83.0, 78.9, 75.9, 67.5, 66.8, 66.7, 56.9, 41.2, 37.4, 36.9, 34.4, 30.6, 26.9, 26.2, 26.0, 24.0, 19.3, 18.5, 18.4, 13.6 (2C), 11.1, −3.3, −4.2, −5.2, −5.3; $[\alpha]_D^{22}$ +20.0 (c 0.37, CH_2Cl_2); HRMS (ESI) m/z calcd for $C_{48}H_{84}O_6Si_3Na$ $(M + Na)^+$ 863.5468, found 863.5470; IR (KBr) 3447, 2956, 2929, 2857, 1468, 1254, 1110, 1084, 1026, 836, 776, 703 cm^{-1}.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of spectra for compounds **2**, **3**, **5**−**8**, **12**, **13**, and **15**−**25**, and related compounds **S1**, **S2**, and **S3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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